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The Honorable Christine Todd Whitman
Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on the American Chemistry Council's HPV Test Plan and Robust Summaries for the Low 1,3-Butadiene C4 Category

Dear Administrator Whitman:

The following comments on the American Chemistry Council's (ACC's) test plan for the low 1,3-butadiene C4 category are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than nine million Americans.

We are gratified that some of the issues we have raised regarding the need to eliminate unnecessary tests in previous ACC test plans have been addressed in the test plan for the low 1,3-butadiene C4 category. For example, the current test plan includes the application of diverse data sets to understand toxicity, the incorporation of results from some other chemical categories to reduce testing, and the application of structure-activity relationships (SARs) to avoid testing of different substances. However, the testing and analysis program outlined here still points to programmatic problems with the HPV program and the toxicological analysis of these light hydrocarbons in particular. While there are clear improvements in the application of SARs and inter-industry and inter-program cooperation, we are concerned that some of the improvements are cosmetic and merely bypass–rather than address–previously stated concerns.

The ACC test plan does not propose any additional tests under the U.S. EPA HPV program, but is sponsoring 1-butene under the ICCA HPV program and isobutylene and 2-butene under the OECD SIDS program. The ACC plans to conduct OECD TG 422 on 1-butene and does not plan to conduct any animal tests under the OECD SIDS program. OECD TG 422 is a combined repeat dose, reproductive, and developmental toxicity screening test that kills 400 animals.

This test plan violates the following terms of the October 1999 Agreement among the EPA, industry (including the ACC), health, animal protection, and environmental organizations:

1. In analyzing the adequacy of existing data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there is

sufficient data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested.

2. Participants shall maximize the use of existing and scientifically adequate data to minimize further testing.
3. Participants shall maximize the use of scientifically appropriate categories of related chemicals and structure activity relationships.

8. In analyzing the adequacy of screening data for chemicals that are substances Generally Recognized as Safe (GRAS) for a particular use by the Food and Drug Administration (FDA), participants should consider all relevant and available information supporting the FDA's conclusions….As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant.

Our four main objections to the ACC's test plan are described below.

1. The proposed combination repeat dose/reproductive/developmental test with 1-butene is inappropriate.

1-butene should not be tested for repeat dose, reproductive, neurotoxic, or developmental effects in the EPA HPV program, the ICCA's HPV program, nor the OECD SIDS program, because extensive tests have been performed with this chemical and other similar chemicals, such as butane and 2-butene. Repeating tests with mixtures of these chemicals is not likely to contribute to the understanding of their potential health hazards.

Any further testing on the members of this category is inappropriate. Numerous experiments have been conducted on many of the components of these industrial streams, as well as mixtures of these substances. The high butadiene C4 category and the petroleum gas category already addressed the potential hazards of these and related chemicals. Any additional testing is not likely to expand the understanding of the health and environmental effects of this category of chemicals.

Our most specific concern is that the ACC is proposing additional testing of 1-butene for repeat dose, reproductive, and developmental effects. Studies on mixtures in the petroleum gas category with significant quantities of 1-butene have already been done. Many studies have already been done with compounds similar to 1-butene, including butane and 2-butene, 2-methyl 2-butene, isoprene, 3,3 dimethyl 1-butene, and other C5-diene compounds. In the C5 non-cyclics category, some streams may contain up to 20 percent 2-butene. In the crude butadiene plan, some of the mixtures contain up to 25 percent 1-butene and up to 54 percent 2-butene. In the petroleum gas test plan, gases evaluated include up to 20 percent total butanes. Conducting screening-level tests on mixed composition industrial streams when the toxicity of individual components is already well understood is inappropriate. We have addressed this issue in detail in our previous petroleum gas and crude butadiene comments.[1,2]

Conducting more animal tests on well-characterized compounds with an extensive human epidemiological and toxicological database is also inappropriate. No human or epidemiological data are cited in this test plan, despite the recent comprehensive review of the carcinogenicity of 1,3 butadiene by the Occupational Safety and Health Administration.[3]

The additional testing on the butadiene stream will provide little useful data for use in regulation, industrial

hygiene, or emergency response. The 1,3 butadiene concentration in air is already regulated at very low levels in industrial settings, with a permissible exposure level (PEL) of less than 1 ppm weighted over an eight-hour period. The PEL is based on epidemiological and toxicological analyses of workers and previous animal studies. The crude screening-level tests proposed in this test plan will provide no insight into the regulation of butadiene in the workplace, especially given the extensive toxicological work already being conducted on the metabolism of butadiene in humans. Rather, it is the issues of human metabolism of 1,3 butadiene and the resulting cancer-causing mechanism that need further study and evaluation.

It should also be noted that some of the primary constituents of these industrial streams, such as n-butane and isobutene, are labeled Generally Recognized as Safe (GRAS) by the Food and Drug Administration. The failure to recognize and use the GRAS data specifically violates the EPA's October 1999 Agreement.

2. This test plan reflects an inefficient use of categories.

Although the ACC has developed a defensible category and has coordinated with other HPV sponsors, it does not go far enough in maximizing the use of chemical categories. The composition of the industrial streams in this category closely overlaps with the substances evaluated in the petroleum gas, high C4 butadiene, and the C5 non-cyclics categories. A thoughtful analysis of all information presented in the robust summaries for these other categories is sufficient for understanding the toxicity of the compounds in the low C4 butadiene category.

The biochemical mechanism of 1-butene metabolism is well understood and quite similar to other compounds, and many tests have been done on mixtures containing 1-butene and 2-butene. Because many of the C4 and C5 compounds are metabolized along the same biochemical pathway, all these compounds compete for the same binding sites. This situation creates the perfect opportunity to apply the PBPK methods of Haddad and Krishnan (1998) and/or the weight of evidence methods of Mumtaz and Durking (1992) in evaluating 1-butadiene toxicity.[4-6] The ACC should capitalize on the opportunity for QSAR analysis and PBPK modeling.

3. With regard to the carcinogenic and reproductive effects of butadiene, the results of animal testing demonstrate the extremely limited use of animal data in predicting potential effects in humans.

High inter-species variability in results of toxicity tests with the components of these industrial streams obscures experimental results and provides minimal insight into potential human toxicity. This problem is especially relevant to toxicity testing of butadiene and related compounds, for which the observed variability of associated adverse effects between mice and rats is on the order of a factor of 1,000. Because of dramatic variability, we question the applicability of any rodent testing on these compounds to the human condition.[7,8]

The documented inter-species variability in response to exposure to these chemicals is so great as to render the results meaningless. The dramatic species differences in adverse health effects following exposure to butadiene are described in great detail in our comments on the high C4 butadiene test plan.

4. In the spirit of the HPV program, sponsors should fully disclose all health effects information and plans to test chemicals. We are concerned that the ACC may be exporting testing plans to other chemical-testing programs to escape public review.

We are concerned that although the ACC proposes no other testing under the HPV program, it instead refers

to new testing proposed under other programs. For example, the ACC plans to test pure 1-butene under the ICCA HPV program. Although the ACC seems confident it will not conduct further animal tests with 2-butene and isobutylene under the OECD SIDS program, we are concerned that this represents a growing trend to export tests to other programs to avoid public scrutiny. By referring indirectly to this other testing, without providing the background regarding the tests or making documents on the testing publicly available, it is impossible to determine the appropriateness of the testing by a third party reviewer.

Furthermore, we are concerned that these tests could be conducted under irrelevant conditions. Many of the similar compounds to 1- and 2-butene have been found to have no toxicological effect at concentrations above 2 to 3 percent in air. As pointed out in the high butadiene C4 plan, the atmosphere of tests conducted at these concentrations is explosive. At this point, the concern for acute toxic effects associated with combustion far outweigh any concern for the potential chronic effects from these gasses. Therefore, tests at these high concentrations are irrelevant and should not be conducted.

In short, while we do recognize that the ACC has attempted to apply thoughtful toxicology in this test plan, the plan includes a proposal for a test that will not change our understanding of the behavior of these chemicals nor the way they are controlled in the workplace. Furthermore, this test plan is repetitive and unnecessary, as all the members of this category could have easily been incorporated into the existing petroleum gas and high C4 butadiene categories.

Thank you for the opportunity to comment and your attention to these important issues. I can be reached via telephone at 202-686-2210, ext. 302, or via e-mail at *ncardello@pcrm.org*. Correspondence should be sent to my attention at the following address: PCRM, 5100 Wisconsin Ave., Suite 400, Washington, DC 20016.

Sincerely,

Nicole Cardello, M.H.S.
Staff Scientist

References

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